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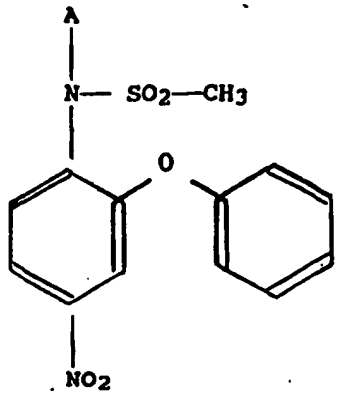
(54) Title: NEW NIMESULIDE SALT CYCLODEXTRIN INCLUSION COMPLEXES

(57) Abstract

Inclusion complexes of nimesulide alkali and alkaline earth salts of general formula (I) where - A stands for an alkali and alkaline earth ion - with cyclodextrins and cyclodextrin derivatives, compositions containing the same, processes for the preparation of the complexes by complexation of nimesulide salts and the compositions as well as methods to use the same as pharmaceuticals.



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New Nimesulide Salt Cyclodextrin Inclusion Complexes

The invention relates to highly soluble, physiologically acceptable inclusion complexes of nimesulide- salts with cyclodextrins, to the preparation thereof, to pharmaceutical compo - sitions containing the same as well as methods for their use.

More particularly the invention relates to inclusion complexes of nimesulide alkali and alkaline earth salts of general formula (I) with cyclodextrins and cyclodextrin derivatives.

In this specification in the general formula
-A always stands for an alkali and alkaline earth ion.

Nimesulide [4-nitro-2-phenoxy-methane-sulfonanilide] is known to be a potent non-steroidal antiinflammatory drug successfully used for the treatment of different painful inflammatory conditions, rheumatoid arthritis and it possesses antipyretic activities too (Belgian Patent N° 801812). Solutions of nimesulide sodium salts were prepared from nimesulide with sodium carbonate in acetone and they were used without isolation as intermediates to prepare N-substituted nimesulide derivatives (Belgian Patent N° 801812). Probably due to the high pH value of their solutions the nimesulide alkali and alkaline earth salts were not used practically as pharmaceuticals. Recently it has been confirmed that based on its mechanism of action in pain relief, nimesulide can be also considered to represent a new type of useful analgesic agents. In case of such drugs a quick onset of action of the orally administered formulation is a very important factor.

Compared to other non-steroidal antiinflammatories, nimesulide has a favorable therapeutic index, minimal acute gastrointestinal toxicity and shows good general tolerability. It is chemically different from other drugs of its class, because its functional acidic group is a sulfonanilide moiety.

Nimesulide is a very hydrophobic drug substance practically insoluble in water, its aqueous solublity is about 0.01 mg/ml at room temperature. The very poor aqueous solubility and wettability of the drug present problems for the preparation of pharmaceutical formulations with good release and non-variable bioavailability.

To overcome the disadvantages connected with the very poor aqueous solubility and wettability the increase of aqueous solubility is an essential aim.

Nimesulide is a weak acid type compound therefore its aqueous solubility in acidic medium, e.g. at the pH of the gastric juice is particularly poor. Orally administered nimesulide is likely to be absorbed only in the lower part of the gastrointestinal tract, probably this explains the rather protracted onset of its biological effect.

Complexation of nimesulide with cyclodextrins is described preferably with ß-cyclodextrin in 1:1 molar ratio whereby faster absorption and higher plasma levels of nimesulide are shown in animal tests as compared with administration of nimesulide per se (Patent Applications PCT/IT91/00043 and DE 4116659).

For solid complex preparation three different known methods are exemplified:
a. precipitation from water and organic solvent mixture by shaking overnight, the preferred solvent being methylene-chloride,
b. freeze- or spray- drying from homogeneous aqueous ammonium hydroxide solution.
c. stirring in aqueous suspension for several days at 60°C and isolating the complex by evaporation under reduced pressure.

Method a. is not acceptable for preparation of CD complexes for pharmaceutical purposes. All organic solvents form more or less stable complexes with cyclodextrins. Inclusion of methylene chloride by ß-cyclodextrin is inevitable in this case, consequently the product might contain a considerable amount of toxic chlorinated solvent. This can not be removed completely even by heating in vacuo at elevated temperature for hours, it will be released only upon dissolution e.g. in the gastric juice. Method c. is the oldest known method for preparation of drug/cyclodextrin-complexes, but the long stirring time, with the concomitant degradation makes this process technically obsolete. Method b. seems to be the best, however it is difficult to completely remove ammonia during the freeze-drying procedure.

In the said Patent Application no data are given about the attainable solubility enhancement of nimesulide with βCD or the dissolution behaviour of the complexes prepared by the three different methods described in the Patent Application.

It can be concluded that both pH alteration towards the alkaline region and complexation with βCD can enhance the solubility of nimesulide. βCD alone shows only a very moderate (about 5-fold) solubility enhancing effect which means 0.05 - 0.06 mg/ml dissolved nimesulide in a saturated aqueous βCD solution. However, significantly higher increase in solubility can be achieved only at pH beyond the physiologically acceptable values.

The object of the present invention was to prepare highly soluble, physiologically acceptable inclusion complexes comprising nimesulide and cyclodextrins. Another object of the invention was to provide efficient method(s) for producing said complexes having the said solubility or redissolving properties.

One object of the present invention are the new inclusion complexes of nimesulide alkali and alkaline earth salt of general formula (I) with cyclodextrins and cyclodextrin derivatives. These new products ensure a considerable 200-600 fold increase in solubility of nimesulide at physiological pH due to the synergetic effect of pH alteration and cyclodextrin complexation.

Preferred embodiments of the invention are inclusion complexes wherein the cyclodextrins and cyclodextrin derivatives are α, β and gamma cyclodextrins, and alkyl or hydroxyalkyl derivatives of cyclodextrin, preferably methyl β-cyclodextrins or hydroxypropyl-β-cyclodextrin.
Further products of preference are inclusion complexes wherein the metal ion in the nimesulide salt is sodium of potassium. Alkaline earth salts e.g. the calcium or magnesium salts might also be used.
A further embodiment of the invention is the process for the preparation of inclusion complexes of nimesulide alkali and alkaline earth salts and cyclodextrins or cyclodextrin derivatives reacting nimesulide alkali and alkaline earth salts in the presence of water with cyclodextrins or cyclodextrin derivatives at pH 7 to 9.5 preferably at pH 7.5 to 8.5.

When carrying out this process it is advantageous to use nimesulide alkali or alkaline earth salts formed in situ in the reaction mixture by adjusting the suspension of nimesulide in water to a pH value of 7 to 9.5 preferably 7.5 to 8.5 by addition of alkali and alkaline earth hydroxides, alkali and alkaline earth carbonates, alkali and alkaline earth hydrogen carbonates, alkali and alkaline earth phosphates, preferably sodium hydroxide, disodium phosphate and/or sodium hydrogen carbonate. Buffers may be used to adjust the desired pH-values.

After formation of the complex water may be removed by freeze-drying, spray-drying, low temperature vacuum evaporation, vacuum drying or other known methods. Aqueous solutions of the complexes or solutions containing the complex formed in situ from the ingredients nimesulide salt and cyclodextrins or cyclodextrin derivatives are also objects of the present invention.

The inclusion complexes according to the present invention were prepared with α, β and gamma-cyclodextrin or with highly soluble hydroxy alkylated and methylated β-cyclodextrin derivatives preferably with randomly methylated β-cyclodextrin, DIMEB or TRIMEB.

The inclusion complexes according to the invention can easily be redissolved in distilled water or physiological saline to obtain clear or slightly opalescent solutions at physiological pH values of 200-600 times higher dissolved nimesulide concentration than its aqueous solubility.

Further objects of the invention are new pharmaceutical compositions containing as active ingredient the highly soluble, physiologically acceptable inclusion complex of nimesulide alkali and alkaline earth salt and cyclodextrins or cyclodextrin derivatives as stated above.

Pharmaceutical compositions of particular importance are those containing as active ingredient the inclusion complex of nimesulide sodium salt and β cyclodextrin. The compositions may contain other pharmaceutically acceptable ingredients such as used for formulation by the pharmaceutical industry.

The complexes and compositions according to the present invention can be used in pharmaceutical formulations administered by oral, parenteral, rectal or topical route. The aqueous solutions of the complexes can also be used in sprays.

A further embodiment of the invention consists in methods of treating patients in need of antiinflammatory and/or analgetic treatment administering to the patient an effective amount of an inclusion complex of cyclodextrins or cyclodextrin derivatives formed with nimesulide alkali and alkaline earth salt.

Most probably the complex - after dissolution in the gastrointestinal tract - is subject to an equilibrium whereby molecularly dispersed nimesulide is formed in the gastric juices , accelerating and improving absorbance and action of the drug.

The invention is illustrated by the following Examples without restricting the scope to their contents.

Examples on chemical synthesis and solubility

Example 1.

Excess amounts of nimesulide were stirred at 30°C in 5 ml samples of distilled water, pH 7.6, 8.0 and 9.6 alkali phosphate buffer solutions containing 0.0, 0.5, 1 and 1.8% (w/v) of β-cyclodextrin. After 18 hours of equilibration the suspensions were filtered across a 0.45 μm membrane filter. The dissolved nimesulide contents of the filtrates were analyzed by spectrophotometry after appropriate dilution with 0.05 N hydrochloric acid in 50% (v/v) ethanol. Absorbance at λ max 300±3 nm was used for quantitative calculation.

Table 1. summarizes the obtained results, whereby final pH values of the filtered solutions are also indicated.

TABLE 1

βCD	Dissolved Nimesulide mg/ml				Final pH of solutions		
%	dist. water	pH 7.6	pH 8.0	pH 9.6	pH 7.6	pH 8.0	pH 9.6
0	0.010	0.034	0.07	0.28	7.40	7.70	8.30
0.5	0.024	0.170	0.26	0.80	-	-	-
1.0	0.035	0.330	0.42	1.27	7.30	7.46	8.09
1.8	0.054	0.570	0.85	1.79	7.24	7.45	7.92

Nimesulide-Na solutions alone and in the presence of equimolar βCD were titrated with 0.1N H_3PO_4. At different pH values the opalescence of the solution became stronger (drug precipitation). Samples are analysed for dissolved nimesulide content by UV spectrophotometry. Figure 2 shows the decrease of nimesulide solubility in the presence and absence of βCD as a function of pH. Dissolved nimesulide in mg/ml is shown against pH values. At around pH 8 almost all nimesulide remains dissolved in presence of βCD while almost the whole drug precipitates from the control solution. (About 10 mg/ml dissolved nimesulide as compared with less than 1 mg/ml). pK_a of nimesulide is shifted to lower value by CD- complexation.

Example 2.
95 g ß-cyclodextrin (0.076 moles, water content 10%) are suspended in 1200 ml of distilled water with vigorous stirring and 12 g (0.038 moles) of nimesulide dissolved in 80 ml of 0.5 N aqueous sodium hydroxide solution are added. When obtaining a homogeneous solution the pH of the solution is adjusted with 0.5 M H_3PO_4 to pH 8.2-8.6 and the yellow solution is feeze-dried to isolate the solid complex. 98 g nimesulide sodium salt/βCD complex of 1:2 molar ratio (a bright yellow fine powder) are obtained. Nimesulide content: 11.8±0.1% measured by UV- spectrophotometry.
Solubility properties of the complex: 100 mg of the product can be dissolved in 3 ml of distilled water resulting in a yellow solution with approximately 4 mg/ml nimesulide content, the solution having a pH value of 7.6±0.1.
DSC curve of the complex is identical with that of the complex obtained according to Example 3 below. Disappearance of the endothermic peak at 240 - 241 °C points to the absence of free nimesulide in the inclusion complex of 1:1 nimesulide sodium-βCD (molar ratio).

Example 3.
33.2 g of ß-cyclodextrin (0.025 moles, water content 13.7%) are suspended in 550 ml of distilled water. 8.25 g of nimesulide (0.025 moles) are dissolved in 60 ml of a 0.5 N aqueous sodium hydroxide solution and added to the suspension of ß-cyclodextrin under vigorous stirring resulting in a clear dark yellow solution. The pH of the solution is adjusted with 0.5 N H_3PO_4

to pH 8.5-8.7 and the solution is freeze-dried to obtain the solid complex.
41 g of nimesulide-sodium salt/βCD complex of 1:1 molar ratio are obtained as a yellow fine powder. Nimesulide content: 20.0±0.2% measured by UV-spectrophotometry.
Solubility properties:
100 mg of the complex can be dissolved in 6 ml of distilled water resulting in a slightly opalescent solution with approximately 3.5 mg/ml nimesulide content, the solution having a pH value of 8.3±0.1.
Differential scanning calorimetry (DSC) curves show characteristic differences between the physical mixture and the lyophilized complex. The sharp endothermic heat flow peak characteristic for the melting of nimesulide appears at 240 - 241 °C on the DSC curve of the physical mixture, followed by a strong exothermic DSC peak characteristic for thermal decomposition of βCD . The DSC pattern of the inclusion complex does not show any endothermic heat flow in the melting range indicating the formation of an inclusion complex between the salt and β-cyclodextrin, only a strong exothermic DSC peak characteristic for thermal decomposition of βCD can be observed.
Figure 3 shows the DSC curves of the nimesulide-sodium : βCD = 1:2 physical mixture (A) and the nimesulide-sodium/βCD complex (B) prepared according to Example 3 : Heat flow (mW) is represented as a function of temperature (°C) [Du Pont 1090 Thermal Analyzer, scanning rate 5°C/min, argone atmosphere].

The nimesulide-potassium salt/βCD complex is prepared according to the same method, using KOH instead of NaOH.

Similarly the nimesulide-calcium and magnesium salt/CD complexes can also be prepared.

Example 4.
30.2 g of β-cyclodextrin (0.024 moles, water content 10%) and 3.75 g of nimesulide (0.012 moles) are suspended in 25 ml of a 0.5 N aqueous sodium hydroxide solution. The thin suspension is stirred by Ultra Turrax high speed dispersing apparatus with r.p.m. approx. 10^3 for five minutes. The pH of the alkaline non-transparent solution is adjusted below pH 9. with 1 N aqueous hydrochloric acid. The solid complex is isolated by dry-

ing at 40°C under vacuo, and the dry complex in powdered.

34 g of nimesulide-sodium salt-βCD comlex (1:2) are obtained as a yellow fine powder. Nimesulide content: 11±0.1% measured by UV-spectrophotometry.

Solubility : 100 mg of the complex dissolved in 3 ml of distilled water resulted in an opalescent solution with approximately 3 mg/ml dissolved nimesulide content, the solution showing a pH value of 7.3±0.1.

Example 5.
40 g of randomly methylated β-cyclodextrin (RAMEB 0.034 moles, average degree of substitution per glucose unit is 1.8) are dissolved in 300 ml of distilled water. 5.4g of nimesulide (0.017 moles) dissolved in 17 ml of 1 N aqueous sodium hydroxide are added whereupon the pH of the solution is adjusted with 0,5 N H_3PO_4 to pH 7.7±0.1. The yellow solution is freeze-dried to isolate the solid complex.

45 g of nimesulide-sodium salt-randomly methylated-β- cyclodextrin (RAMEB) complex of 1:2 molar ratio are obtained in the form of a fine yellow powder. Nimesulide content: 11.1±0.1% measured by UV-photometry.
Solubility: 100 mg of the complex dissolved in 2 ml of distilled water result in a yellow solution (pH 7.3±0.1) with approximately 6 mg/ml nimesulide content.

Example 6.
2.6 g of gamma-CD (0.002 moles) are dissolved in 20 ml of distilled water and 0.308 g (0.001 moles) of nimesulide dissolved in 5 ml of 0.2 N aqueous sodium hydroxide are added whereupon the pH of the solution is adjusted to pH 7.4-7.5, and the yellow solution is freeze-dried. 2.9 g of nimesulide sodium salt/gamma-CD complex of 1:2 molar ratio are isolated in the form of a very fine yellow powder. Nimesulide content: 10.5 ± 0.2% measured by UV-photometry. 100 mg in 2 ml of distilled water give a clear yellow solution with approximately 5 mg/ml nimesulide content (pH= 7.3 ± 0.1).

Example 7.

13 g of hydroxypropylated βCD (0.01 mole average degree of substitutaion per glucose unit is 2.7) are dissolved in 150 ml of distilled water and 1.54 g of nimesulide (0.005 M) and 5 ml of 1N sodium hydroxide are added while stirring. A dark clear yellow solution is obtained the pH of which is adjusted to 7.5 ± 0.1 with 0.2 N phosphoric acid, and the solution is freeze-dried.
14 g of nimesulide sodium/HPβCD complex of 1:2 molar ratio are obtained in the form of a very fine yellow powder.
Nimesulide content: 10.6 ± 0.2% measured by UV photometry.
100 mg of this complex dissolved in 2 ml of distilled water resulting in a clear yellow solution with about 5 mg/ml dissolved nimsulide content (pH of the solution = 7.4 ± 0.1).

Example 8.
The dissolution of nimesulide-Na/βCD complex prepared according to Example 2 was compared to nimesulide-Na and nimesulide-Na/βCD complex prepared in situ from the corresponding 1:2 molar physical mixture of the components. Simulated gastric juice was used as a medium. 100 mg of nimesulide, an equivalent amount of the isolated complex and the physical mixture of the ingredients were stirred in 20 ml of pH 1.4 aqueous HCl solution. Samples were taken at 2, 15 and 60 minutes. On filtration the nimesulide content was measured by UV photometry. Average results of three experiments are summarized in Table 2.

Table 2.

time (min)	Concentration of Dissolved Nimesulide (μg/ml) Nim.-Na	Nim.-Na/βCD isolated complex	Nim.-Na/βCD in situ complex
2	5.4 ± 0.7	35.4 ± 1.4	33.3 ± 2.2
15	4.0 ± 0.1	36.1 ± 0.25	33.3 ± 0.3
60	4.4 ± 0.5	34.6 ± 1.5	35.1 ± 0.2

The measurable nimesulide concentration both for the isolated complex and the in situ formed complex are approximately five times higher than in the case of nimesulide-Na substance. This higher concentration is maintained even after 60 minutes. The results indicate that in situ complex formation from the physical mixture took place under the conditions employed.

Example 9.
A comparative solubility test was carried out using nimesulide-

Na/βCD complex tablets (100 mg), Mesulid commercial tablets (batch N° 891 1026/SCAD 91/11. 100 mg) and nimesulide-Na salt substance (prepared by lyophilization from a solution of 1:1 molar ratio nimesulide and sodium hydroxide, using an equivalent amount to 100 mg of nimsulide).

Powdered tablets of each sample were suspended in 20 ml of pH 1.4 aqueous HCl solutions and stirred at ambient temperature. Samples were taken after 2, 60 and 90 minutes. On filtration the nimesulide concentration of the filtrates was evaluated by UV- spectrophotometry after dilution with 96% ethanol. Absorbance at λmax = 299 ± 1 nm was used for quantitative calculation taking $E^{1\%}_{1cm}$ 299 ± 1 nm = 257 for nimesulide. Results are summarized in Table 3.

Table 3.

Nimesulide concentrations as a function of time at pH = 1.4

	Nimesulide conc. (μg/ml)		
	2 min.	60 min.	90 min.
Nim.-Na/βCD tbl.	35	43	37
Mesulid tbl.	10	14	11
Nim.-Na salt	7	10	6

Table 3. shows that considerable solubility differences are found in favour of the complex tablets. It is obvious that the solubility of an acid type drug might be lower in a pH 1.4 solution than in water. The alkali salts of the drug are freely soluble in water. Their in vivo absorption however after oral administration is delayed owing to the precipitation of the acid-form under the pH of the stomach.

βCD complexation enhances solubility of nimesulide also under acidic pH conditions. Based on the above in vitro findings an improved absorption of nimesulide-salt complexes is understood after oral administration because the solubility under acidic pH is a necessary precondition e.g. for faster onset of action.

Example 10.

2.3 g of βCD (0.002 moles, water content 14%) and 0.31 g of nimesulide (0.001 mole) are suspended in 100 ml of distilled water. 2 ml of 0.5N aqueous potassium hydroxide are added while stirring. pH of the dark yellow solution obtained is adjusted below 9 using 0.5N hydrochloric acid. 2.8g of nimesulide-K/βCD

complex (1:2) are isolated by freeze-drying. Nimesulide content: 10.8 ± 0.2% (UV spectr.)
Solubility: 100 mg of the above complex are dissolved in 3 ml of distilled water. A clear or slightly opalescent solution with ≈ 3mg/ml dissolved nimesulide results, pH 7.8 ± 0.1.

Examples on Pharmaceutical Compositions.

Example 11.

Composition of tablets with 50 mg and 100 mg of nimesulide content:

nimesulide-sodium salt/βCD complex (Example 3)	250 mg	500 mg
calcium phosphate	60 mg	85 mg
lactose	35 mg	45 mg
magnesium-stearate	5 mg	5 mg
Total	350 mg	540 mg

The complex is homogenized with the additives and directly pressed into tablets.

Example 12.

Composition of granule sachet formulation with 50 mg and 100 mg of nimesulide content of each.

nimesulide-sodium salt/βCD	450 mg	900 mg
sorbite	2500 mg	4000 mg
lemon flavour	15 mg	30 mg
saccharine	5 mg	5 mg
Total	2970 mg	4935 mg

The complex is homogenized with sorbite and additives and filled into sachets.

Example 13.

Composition of oral liquid formulation with 50 mg/10 ml nimesulide content

nimesulide-K/βCD complex (Ex 3.)	2.500 g
hydroxypropyl cellulose	0.200 g
potassium sorbate	0.150 g
fructose	5.0 g
saccharine sodium	qu.sat.
demineralized water	ad 100.0 ml

The viscosity enhancer is dissolved in about 80 ml of warm demineralized water and the complex added and dissolved. Other addi-

tives are added to obtain a homogeneous solution. Each spoon (~10 ml) contains 50 mg of nimesulide.

Example 14.
Composition of ointment with 10 mg/1 g nimesulide content:

Complex of Example 5		9 g
hydrophilic ointment		91 g
	Total	100 g

The hydrophilic ointment base is melted at 50-60°C and the nimesulide-salt complex is added under stirring to obtain a homogeneously dispersed system. Under continuous stirring the ointment is cooled to room temperature and put into containers of 100 g.

Example 15.
Composition of a parenteral formulation containing 5 mg/ml of nimesulide sodium salt-gamma-CD complex:

Complex of Example 6		500 mg
sodium chloride		81 mg
distilled water for injections	ad	10 ml

Proper volumes of the complex solution are filled into containers with 50 mg nimesulide content each and lyophilized. Before use the lyophilized powder is dissolved with distilled water.

Example 16.
Composition of suppository containing 50 mg of nimesulide:

Complex of Example 3		250 mg
polyethylene glycol-suppository base		1250 mg
	Total	1500 mg

The complex is homogenized with the melted suppository base and formulated to give suppositories.

Example 17.
Hard gelatine capsules used for in situ complexes:

nimesulide-Na	53.5 mg	107 mg
βCD	214 mg	428 mg
Mg stearate	2.5 mg	5 mg
Total	270 mg	540 mg

The complex is formed when dissolving the capsule in acidic medium or after administration in the gastrointestinal tract.

CLAIMS

1.
Inclusion complexes of nimesulide alkali and alkaline earth salts of general formula (I) where
- A stands for an alkali and alkaline earth ion -
with cyclodextrins and cyclodextrin derivatives.

2.
Inclusion complex of nimesulide sodium, potassium, magnesium or calcium salt with ß-cyclodextrin or gamma cyclodextrin the molar ratio of the salt to cyclodextrin being 1:1 or 1:2.

3.
Inclusion complex according to claim 1 wherein the cyclodextrins and cyclodextrin derivatives are α, ß and gamma cyclodextrins, and/or alkyl or hydroxyalkyl derivatives of cyclodextrin, preferably methyl ß-cyclodextrins or hydroxypropyl-ß- cyclodextrin.

4.
Inclusion complex according to claim 1 wherein the nimesulide alkali is nimesulide sodium salt.

5.
Process for the preparation of inclusion complexes of nimesulide alkali and alkaline earth salts and cyclodextrins or cyclodextrin derivatives c h a r a c t e r i z e d b y reacting nimesulide alkali and alkaline earth salts in the presence of water with cyclodextrins or cyclodextrin derivatives at pH 7 to 9.5 preferably at pH 7.5 to 8.5.

6.
Process according to claim 5 c h a r a c t e r i z e d by using nimesulide alkali and alkaline earth salts formed in situ in the reaction mixture by adjusting the suspension of nimesulide in water to a pH value of 7 to 9.5 preferably 7.5 to 8.5 by addition of alkali and alkaline earth hydroxides, alkali and alkaline earth carbonates, - hydrogen carbonates, - phosphates, preferably sodium hydroxide, disodium phosphate and/or sodium hydrogen carbonate or other buffers.

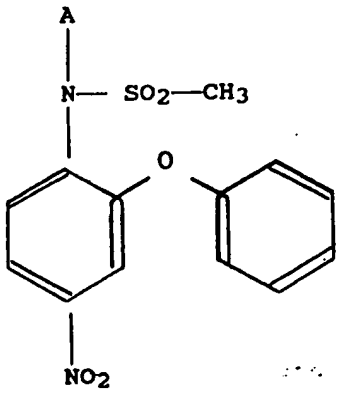

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FIGURE 1.

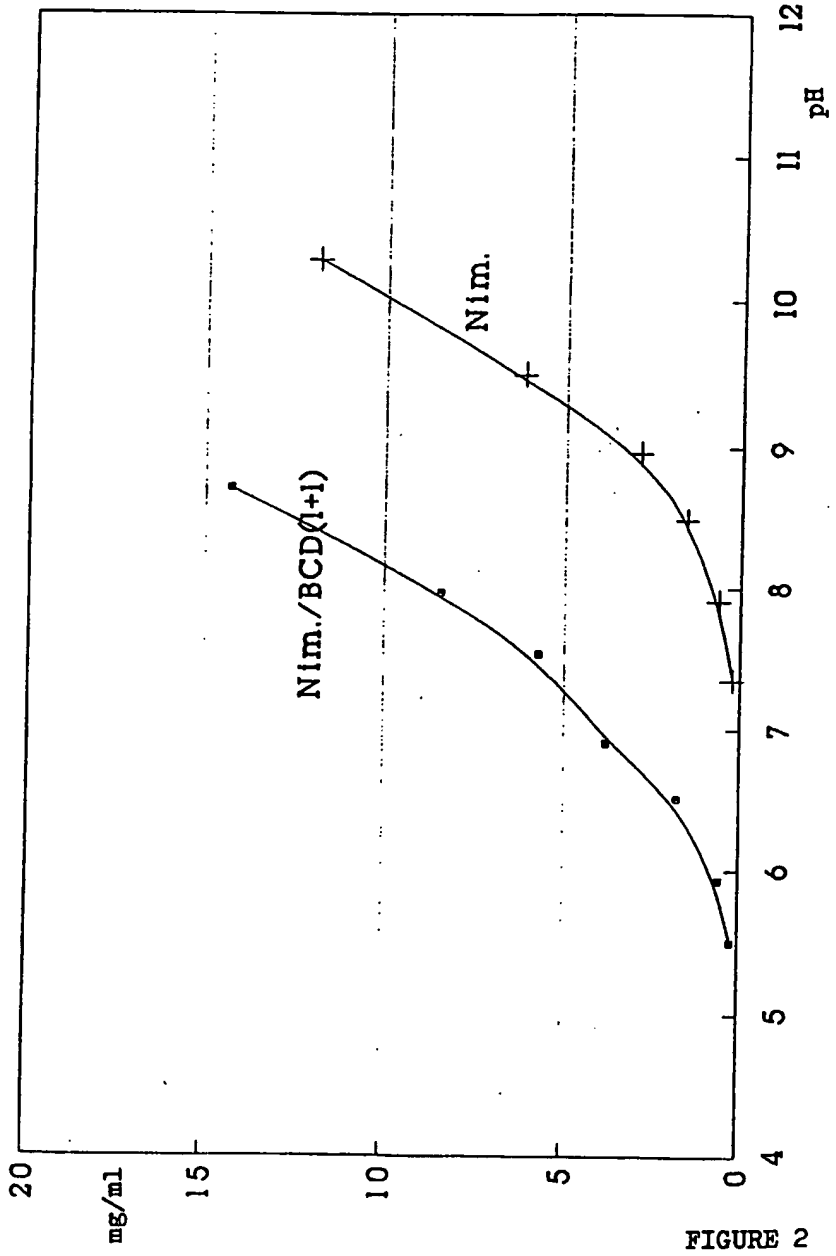
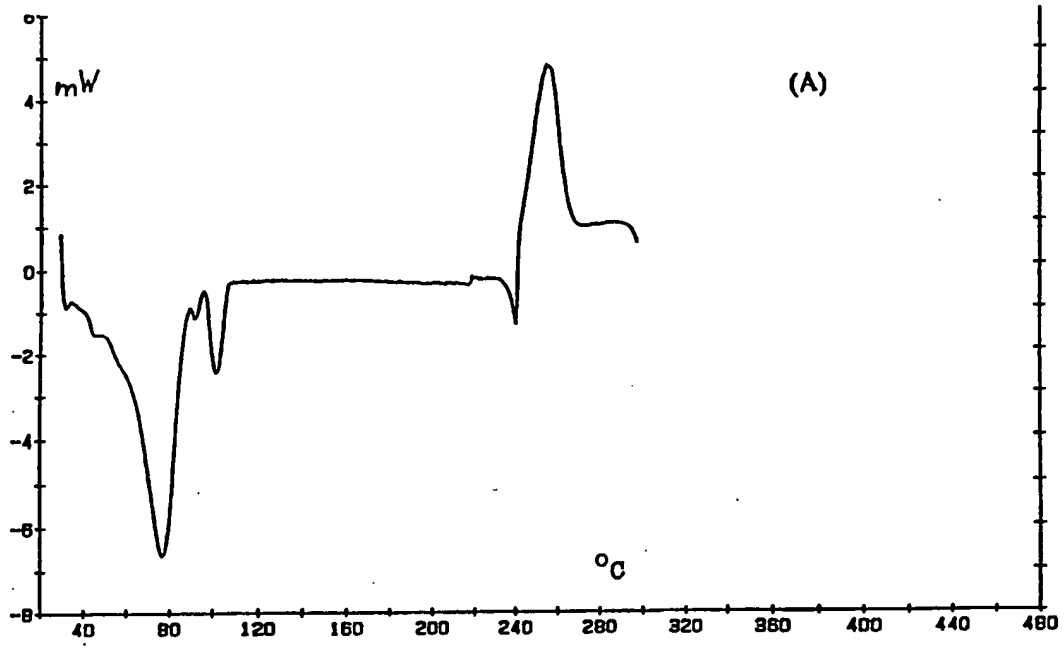


FIGURE 2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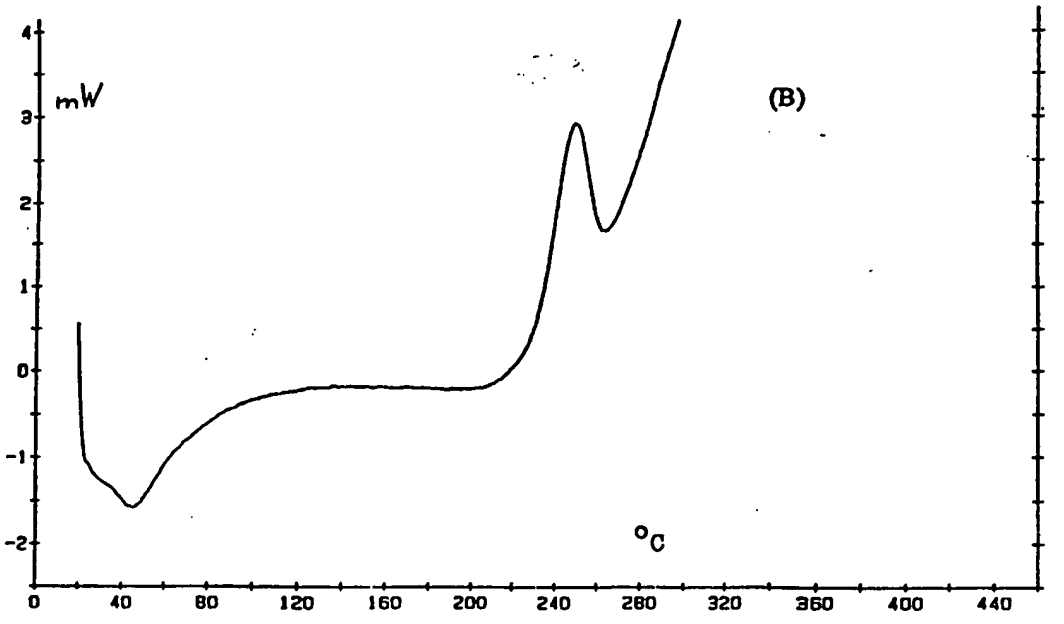
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80
120
160
200
240
280
320
360
400
440

FIGURE 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU 94/00014

A. CLASSIFICATION OF SUBJECT MATTER

IPC[5]: C 08 B 37/16; A 61 K 47/40, 31/63

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[5]: C 08 B; A 61 K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO, A1, 91/17 774 (BOEHRINGER INGELHEIM ITALIA S.P.A.) 28 November 1991 (28.11.91), claims. (cited in the application; & DE, A1, 4 116 659).	1-3,5,7-11
A	US, A, 5 019 563 (HUNTER et al.) 28 May 1991 (28.05.91), column 1, line 63 - column 2, line 49.	

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 September 1994 (21.09.94)	29 September 1994 (29.09.94)
Name and mailing address of the ISA/AT AUSTRIAN PATENT OFFICE Kohlmarkt 8-10 A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer Hauswirth e.h. Telephone No. 1/53424/136

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU 94/00014

Interoffice memo:

Additionally to WO, A1, 91/17 774 (cited in the application) no further relevant documents could be retrieved.
US, A, 5 019 563 was cited merely to show an analogous process, i.e. the preparation of alkali and alkaline earth salt complexes with cyclodextrins in order to achieve improved water-solubility characteristics of the end-product.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/HU 94/00014

In Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
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Form PCT/ISA/210 (patent family annex) (July 1992)